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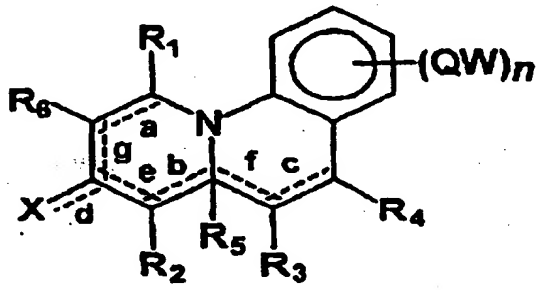
(54) Title: BENZO[C]QUINOLIZINE DERIVATIVES, THEIR PREPARATION AND USE AS 5α-REDUCTASES INHIBITORS

(57) Abstract

The present invention refers to benzo[c]quinolizine derivatives of general formula (I), their pharmaceutically acceptable salts or esters, processes for their preparation and pharmaceutical compositions containing them.



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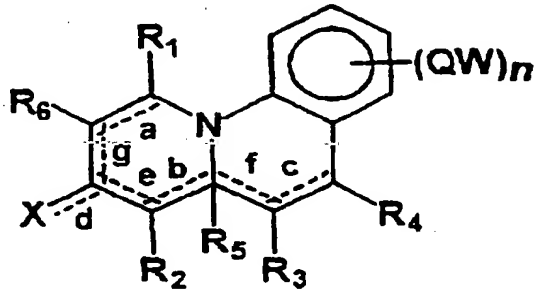
Benzo[c]quinolizine derivatives, their preparation and use as 5α-reductases inhibitors.

Field of the invention

The present invention refers to benzo[c]quinolizine derivatives of general formula (I)



(I)

wherein:

R_1, R_2, R_3, R_4, R_6, same or different, are chosen in the group consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, heterocycle, halogen, CN, azide, NRR', C_{1-8}alkylamino, arylamino, C_{1-8}alkyloxy, aryloxy, COOR, CONRR' wherein R and R', same or different, are chosen in the group consisting of: H, C_{1-8}alkyl, cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl;

R_5 is chosen in the group consisting of: H, C_{1-8}alkyl, COOR, CN, aryl, heterocycle;

X is chosen in the group consisting of: O, C(=O)R, COOR, NO_2, CONR'R wherein R and R' are as above defined;

Q is chosen in the group consisting of: simple bond, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, CO, CONR, NR, wherein R is as above defined;

W is chosen in the group consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, trifluoromethyl, C_{1-8}alkoxy, C_{1-8}alkoxy-C_{1-}

$_8$alkyl, arylC_{1-8}alkyl, aryl, aryloxy, arylamino, C_{1-8}alkylcarbonyl, arylcarbonyl, halogen, CN, NRR', C_{1-8}alkylamino, heterocycle wherein the groups alkyl, alkenyl, alkinyl, cycloalkyl, aryl, heterocycle, can be substitued;

n is an integer comprised between 1 and 4;

the symbol ----- means that the corresponding bonds a, b, c, d e, f, and g can be simple or double bonds;

with the proviso that when b or f are a double bond then the group R_5 is absent;

their pharmaceutically acceptable salts or esters, their process of preparation and their use as inhibitors of steroid 5α-reductases (hereinafter indicated as 5α-reductases).

State of the art

The enzyme known as steroid 5α-reductase is a system formed by two iso-enzymes (type I and type II or 5αR-I and 5αR-II respectively)) which converts testosterone into dihydrotestosterone, the most powerful androgen circulating in the body.

The type I iso-enzyme (5αR-I) is mainly present in liver and skin while the type II iso-enzyme (5αR-II) is mainly present in the prostate tissue and in the male sexual organs and its activity is essential in the fetal developping process for the differentiation of the external sexual organs.

The production of dihydrotestosterone is associated with some pathologies which are widely diffused as for example benign prostate hypertrophy, prostate cancer, baldness and acne in men and hirsutism in women. More particularly iso-enzyme I plays a role in the pathologies regarding the skin while iso-enzyme-II is involved in

wherein the substituents R_1, R_2, R_3, R_4, R_5, R_6, X, Q, W, n and the symbol ----- are as above defined.

According to the present invention with group C_{1-8}alkyl, C_{2-8}alkenyl and C_{2-8}alkinyl are indicated linear or branched alkyl radicals as for example: methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, ethylene, propene, butene, isobutene, acetylene, propine, butine ecc.

With cycloalkyl are indicated: cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane.

With aryl are indicated: phenyl and naphtyl.

Heterocycle means in particular: saturated or aromatic heterocycles containing one or more N atoms, more particularly: piridine, imidazole, pyrrole, indole, triazoles, pyrrolidine, piperidine.

Halogen means: fluorine, chlorine, bromine, iodine.

The substituents of the above said group W are preferably: halogen, OR, phenyl, NRR', CN, COOR, CONRR', C_{1-8}alkyl (wherein R and R' are as above defined).

In particular, according to the present invention compounds of formula (I) are preferred wherein:

R_5 = H, heterocycle

X = O

Q = simple bond, CO, CONR, NR (wherein R is as above defined)

W = H, F, Cl, Br, Me, t-butyl, C_{1-8}alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl-C_{1-8}alkyl, C_{1-8}alkylcarbonyl, phenylcarbonyl.

prostate pathologies.

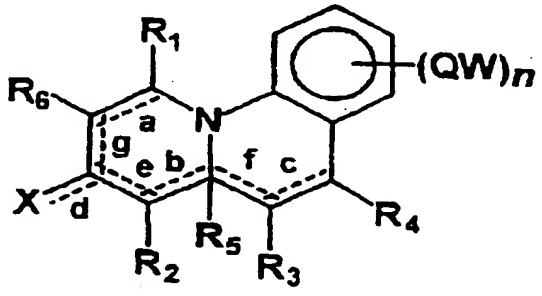
In the recent years a lot of international searchers have tried to isolate new compounds capable of inhibiting the 5α-reductase enzyme in order to treat the above said pathologies, especially, if possible, acting selectively on only one of the two iso-enzymes.

Inhibitors of 5α-reductase, and also of the iso-enzymes 5αR-I and 5αR-II were already described, for example finasteride used with success in the treatment of benign prostate hypertrophy [see for example J.Med.Chem. 36, 4313-15 (1993), J.Med.Chem. 37, 3871-74 (1994)]. It is therefore evident the importance of developing new compounds capable of inhibiting the action of the 5α-reductase enzyme and in particular capable of acting selectively on 5αR-I iso-enzyme which, as said, is responsible, of widely diffused pathologies having an high impact as baldness in men and hirsutism in women.

Detailed description of the invention

The present invention refers to new compounds capable of inhibiting the 5α-reductase enzyme, either selectively in respect of 5αR-I and 5αR-II or on both the iso-enzymes, useful for the treatment of the pathologies mediated by the enzyme.

The products according to the invention have general formula (I)

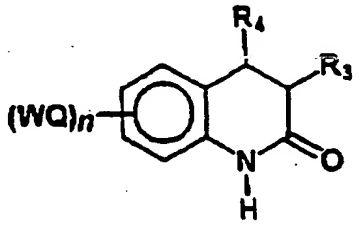


(I)

and (trans);

8-chloro-4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis) and (trans).

The compounds according to the present invention can be prepared for example starting from compounds of formula 2



(2)

(2)

wherein R_3, R_4, W, Q and n are as above defined, following the reaction Scheme reported hereinafter.

The compounds 2 are commercialy available or can be prepared according to known techniques.

As it can be seen from the Scheme the preparation of the compounds according to the invention involves the protection of the amide-group in compound 2 by the protecting group Z, for example tert-butoxycarbonyl (t-Boc), to give compound 3; compound 3 is reduced to compound 4, for example (when R_5 is H) with sodium borohydride in ethanol (pH 3), which is reacted with a silylether 6, produced "in situ" starting from vinyl-ketones 5 (wherein R_1, R_2 and R_6 are as above defined) with a silylating agent as trimethylsilyltrifluorometansulphonic anhydride (TMSOTf) and thereafter hydrolized, for example in sodium hydrogencarbonate, to give the compounds of formula (I) wh rein X = O. The possible introduction of the double bonds and the transformation of the group X

n = 1 and 2

R_1, R_2, R_3, R_4, R_6 = H, Me, CN, phenyl, COOR, CONRR' (wherein R and R' are as above defined).

Among the pharmaceutically acceptable esters and salts according to the present invention the following can be mentioned: hydrochloride, sulphate, citrate, formiate, phosphate.

Preferred compounds according to the present invention are:

1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;

8-chloro-1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;

1,2,4,4a,5,6 hexahydro-8-methyl-(11H)-benzo[c]quinolizine-3-one;

1,2,4,4a,5,6 hexahydro-4-methyl-(11H)-benzo[c]quinolizine-3-one;

1,2,4,4a,5,6 hexahydro-1-methyl-(11H)-benzo[c]quinolizine-3-one;

1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

8-chloro-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

8-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

1-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

5,6-dihydro-(11H)-benzo[c]quinolizine-3-one;

8-chloro-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

8-chloro-1-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one;

8-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

4-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis) and (trans);

8-chloro-4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

4,8-dimethyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

4,8-dimethyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis)

in one of the other groups mentioned above can be easily performed according to known techniques starting from the corresponding compound of formula (I) obtained as indicated. For example the introduction of the double bonds in position a or b, can be performed by reaction of dichlorodicyanoquinone (DDQ) with the corresponding silylenolethers or by oxidation with mercuric acetate of the saturated corresponding compound obtained as described above. The transformation of group X can be performed via the corresponding enoltriflates and their carbonylation in the presence of palladium diacetate, triphenylphosphine and the suitable nucleophilic reagent (alcohol, amine, nitro-group).

Example 1

Preparation of N-(t-butoxycarbonyl)-3,4-dihydroquinolin-2(1H)-one [compound 3 wherein $(QW)_n$ = H, R_3 = R_4 = H]

5 g (34 mmoles) of 3,4-dihydroquinolin-2(1H)-one [compound 2 wherein $(QW)_2$ = H, R_3 = R_4 = H] and 111 ml of CH_2Cl_2 are charged, under nitrogen, in a 250 ml round bottom flask, equipped with magnetic stirrer.

To the above said mixture 4.7 ml (34 mmoles) of triethylamine (distilled on KOH), 8.9 g (40.8 mmoles) of di-butyl dicarbonate and 1 g (8.2 mmoles) of 4-dimethylaminopyridine are added. The mixture is stirred under reflux for 5 h, then for one night at room temperature and thereafter the solvent is removed and 200 ml of water are added. The aqueous phase is extracted with diethylether and the organic phase is neutralized with an aqueous solution of $KHSO_4$ (1 M). The organic phase is washed with a saturated solution of NaCl and dried on Na_2SO_4. After filtration and removal of the solv nt 8.23 g of the desired

product are obtained (white crystals). M.p.: 68 - 69°C. Yield: 98%.

Example 2

Preparation of N-(t-butoxycarbonyl)-2-ethoxy-1,2,3,4-tetrahydroquinoline [compound 4 wherein $(QW)_n$ = H, $R_3 = R_4 = R_5$ = H].

4.35 g (17.6 mmoles) of the compound obtained from example 1 and 136 ml of absolute ethanol are charged in a 500 ml round bottom flask equipped with magnetic stirrer.

The solution is cooled at -25°C and 2.66 g (70.4 mmoles) of $NaBH_4$ (subdivided in 6 portions) are added to the mixture in 1 h. After 4 h a solution of HCl 2N in absolute ethanol is added to the mixture, up to pH 3, and the mixture is stirred at 0°C for 1.5 h. 100 ml of water are added, the aqueous phase is extracted with methylene chloride, the organic phase is washed with a saturated solution of $NaHCO_3$ and a saturated solution of NaCl and the mixture is dried on Na_2SO_4. After filtration the solvent is removed and 4,74 g of the expected product are obtained (dense yellow liquid); yield 96%.

Operating as above said other compounds 4 wherein the substituents can not be reduced by $NaBH_4$ are obtained; if substituents which could be reduced by $NaBH_4$ are present these must be previously protected.

Example 3

Preparation of 1,2,4,4a,5,6-hexahydro-(11H)-benzo[c]quinolizin-3-one [compound of formula (I) wherein X = O; $(QW)_n$ = H; $R_1 = R_2 = R_3 = R_4 = R_5 = R_6$ = H; a,b,c,e,f,g = simple bond]

70 µl (0.86 mmoles) of 3-buten-2-one [compound of formula 5 wherein $R_1 = R_2 = R_6$ = H] and 2 ml of anhydrous CH_2Cl_2 are charg d, at 0°C under argon in a two-necked round bottom flask equipped with magnetic stirrer and dropping funnel.

170 µl (1.22 mmoles) of triethylamine (distilled on KOH) and 209 µl (1.08 mmoles) of trimethylsilyltrifluorometansulphonate (TMDOTf) (drop by drop) are added to the mixture. In this conditions 2-(trimethylsilyloxy)-1,3-butadiene [compound 6 wherein R_1 = R_2 = R_6 = H] is formed "in situ". The mixture is stirred for 45 minutes and thereafter a solution of 100 mg (0.36 mmoles) of the product from Example 2 in 2 ml of anhydrous CH_2Cl_2 is added therein, drop by drop, together with 69 µl (0.36 mmoles) of TMSOTf. The mixture is brought to room temperature and after 30 minutes 4 ml of a saturated solution of $NaHCO_3$ are added and the mixture is stirred vigorously for 36 h.

4 ml of water are added to the mixture and the aqueous phase is extracted with methylene chloride, the organic phase is washed with a saturated solution of $NaHCO_3$, water, a saturated solution of NaCl and is dried on Na_2SO_4. After filtration the solvent is removed and 59 mg of crude product are obtained. The product is purified by flash chromatography on silica gel column (FCC) eluting with methylene chloride and triethylamine 1%. 18 mg of the wanted product are obtained (crystals). M.p.: 53 - 54°C. Yield 25%.

Using various vinyl-ketones 5, or using directly the various silylenolethers 6 (when available), it is possible to prepare the corresponding derivatives of formula (I).

In particular when 1-methoxy-3-(trimethylsilyloxy)-1-3-butadiene (compound 6 wherein R_1 = MeO, R_2 = H, R_6 = H) was used, 4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one (compound I wherein X = O, $(QW)_n$ = H, R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H, a = double bond; b,c,e,f,g = single bond] was directly obtained according to the synthesis described in the following Example 4.

Example 4

Preparation of 4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one [compound I wherein X = O, $(QW)_n$ = H; R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H; a = double bond; b,c,e,f,g = single bond].

To a stirred solution of compound 4 [$(QW)_n$ = H, R_3 = R_4 = H] (4 g, 14.42 mmol) of the example 3, in 75 ml of anhydrous CH_2Cl_2 under argon at -10°C is added, dropwise in 7 min, 28.84 ml of a 1M solution of $TiCl_4$ in CH_2Cl_2 maintaining the temperature below -5°C. Then 1-methoxy-3-(trimethylsilyloxy)-1-3-butadiene (compound 6, R_1 = MeO, R_2 = H, R_6 = H) (3.29 ml, 17.3 mmol) is added by syringe at 0°C, and the reaction was left aside at room temperature for 1 h. The reaction mixture is added, cautiously, with 100 ml of $NaHCO_3$ satured solution, and then stirred for 30 min. The organic layer is separated, washed with water, filtered on Celite and dried over Na_2SO_4. After removal of the solvent the crude product is purified by flash column chromatography (eluant light-petroleum ether/ethyl acetate 1:4) affording 0.72 g (25% yield) of the expected product (white crystals, m.p.: 135-137°C).

Example 5

a) Preparation of 4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein X = O; $(QW)_n$ = H; R_1 = R_3 = R_4 = R_5 = R_6 = H; R_2 = Me; a = double bond; b,c,e,f,g = single bonds], 4 methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein X = O; $(QW)_n$ = H; R_1 = R_3 = R_4 = R_6 = H; R_2 = Me; b = double bond; a,c,e,f,g = single bonds] and 4-methyl-5,6-dihydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein X = O; $(QW)_2$ = H; R_1 = R_3 = R_4 =

R_6 = H; R_2 = Me; a,b = double bonds; c,e,f,g = single bonds].

1 g (4.64 mmol) of 4-methyl-1,2,4,4a,5,6-hexahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I), wherein X = O; $(QW)_n$ = H; R_1 = R_3 = R_4 = R_5 = R_6 = H; R_2 = Me; a,b,c,e,f,g = single bonds, obtained according to example 3 by reaction of compound 4 (wherein $(QW)_n$ = H; R_3 = R_4 = R_5 = H) of example 2 and ethylvinylketone (compound 5 wherein R_1 = R_6 = H; R_2 = Me] and 120 ml of 5% solution (v/v) of glacial acetic acid in water are charged under nitrogen in a two-necked round bottom flask, equipped with magnetic stirrer, refrigerator and dropping funnel. Under vigorous stirring, 7.27 g (18.56 mmol) of tetrasodic salt EDTA and 5.92 g (18.56 mmol) of $(CH_3CO_2)_2Hg$ are added and the reaction mixture is heated at 90°C for 2h. After cooling at room temperature the reaction mixture is added with 120 ml of water and extracted with methylene chloride (4x70 ml). The separated organic phase is washed with a satured solution of $NaHCO_3$, with a satured solution of NaCl then dried over Na_2SO_4. After removal of the solvent the crude product is purified by flash chromatography on silica gel by elution with ethylacetate/light petroleum ether 2:1 affording:

83 mg (10%) (gummy solid) of cis-4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein X = O; $(QW)_n$ = H; R_1 = R_3 = R_4 = R_5 = R_6 = H; R_2 = Me; a = double bond; b,c,e,f,g = single bonds]

350 mg (40%) (crystals, m.p.: 148-150°C) of 4 methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein X = O; $(QW)_n$ = H; R_1 = R_3 = R_4 = R_6 = H; R_2 = Me; b = double bond; a,c,e,f,g = single bonds] and

107 mg (12%) (gummy solid) of 4-methyl-5,6-dihydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein X = O; $(QW)_n$ = H; $R_1 = R_3 = R_4 = R_6$ = H; R_2 = Me; a,b=double bonds; c,e,f,g = single bonds].

Activity Test

The inhibition potency of the prepared compounds in respect of the iso-enzymes 1 and 2 of 5α-reductase was determined using tissue samples (for example prostate human tissue) or human cellular systems (for example DU 145 cells) expressing iso-enzymes 2 and 1 respectively.

The samples are incubated in the presence of testosterone labelled with tritium and thereafter the quantity of labelled dihydrotestosterone formed in the absence and in the presence of the inhibitor is measured.

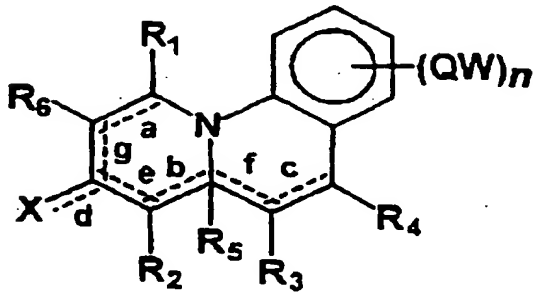
The compounds showed high inhibiting power of 5α-reductase enzyme (in particular of iso-enzyme 1) with an inhibition higher than 50% at the concentration of 10 - 100 nM.

For the therapeutical administration the compounds according to the invention are prepared in the form of pharmaceutical compositions containing the active principle and the organic or inorganic excipients suitable for the oral, parenteral or topic administration of the compositions. The pharmaceutical compositions can thererfore be in the solid form (dragees, suppositories, creams, ointments), liquid form (solutions, suspensions, emulsions) and can possibly contain the stabilizers, conservatives, humectants, emulsifier, buffers or salts used for equilibrating the osmotic pressure which are commonly used in the art.

Generally the administration of the compounds is performed according to the modalities and quantities observed for the known agents used for the same purposes and taking into consideration the age and conditions of the patients.

Claims

1 1. Benzo[c]-quinolizine compounds of formula (I)



(I)

2 wherein:

3 R_1, R_2, R_3, R_4, R_6, same or different, are chosen in the group
4 consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl,
5 aryl, heterocycle, halogen, CN, azide, NRR', C_{1-8}alkylamino,
6 arylamino, C_{1-8}alkyloxy, aryloxy, COOR, CONRR' wherein R and R', same
7 or different, are chosen in the group consisting of: H, C_{1-8}alkyl,
8 cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl;
9 R_5 is chosen in the group consisting of: H, C_{1-8}alkyl, COOR, CN, aryl,
10 heterocycle;
11 X is chosen in the group consisting of: O, C(=O)R, COOR, NO_2, CONR'R
12 wherein R and R' are as above defined;
13 Q is chosen in the group consisting of: simple bond, C_{1-8}alkyl, C_{2-}
14 $_8$alkenyl, C_{2-8}alkinyl, cycloalkyl, CO, CONR, NR, wherein R is as above
15 defined;
16 W is chosen in the group consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-}
17 $_8$alkinyl, cycloalkyl, trifluoromethyl, C_{1-8}alkoxy, C_{1-8}alkoxy-C_{1-}
18 $_8$alkyl, arylC_{1-8}alkyl, aryl, aryloxy, arylamino, C_{1-8}alkylcarbonyl,
19 arylcarbonyl, halogen, CN, NRR', C_{1-8}alkylamino, heterocycle wherein
20 the groups alkyl, alkenyl, alkinyl, cycloalkyl, aryl, heterocycle, can

be substitued;

n is an integer comprised between 1 and 4;

the symbol ----- means that the corresponding bonds a, b, c, d e, f, and g can be simple or double bonds;

with the proviso that when b or f are a double bond then the group R_5 is absent;

their pharmaceutically acceptable salts or esters.

2. Benzo[c]-quinolizine compounds of formula (I)

R_5 = H, heterocycle

X = O

Q = simple bond, CO, CONR, NR (wherein R is as above defined)

W = H, F, Cl, Br, Me, t-butyl, C_{1-8}alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl-C_{1-8}alkyl, C_{1-8}alkylcarbonyl, phenylcarbonyl.

n = 1 and 2

R_1, R_2, R_3, R_4, R_5, R_6 = H, Me, CN, phenyl, COOR, CONRR' (wherein R and R' are as above defined).

3. Benzo[c]-quinolizine compounds according to Claim 1 of formula

1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;

8-chloro-1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;

1,2,4,4a,5,6 hexahydro-8-methyl-(11H)-benzo[c]quinolizine-3-one;

1,2,4,4a,5,6 hexahydro-4-methyl-(11H)-benzo[c]quinolizine-3-one;

1,2,4,4a,5,6 hexahydro-1-methyl-(11H)-benzo[c]quinolizine-3-one;

1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

8-chloro-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

8-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

1-methyl-1,2,4,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

5,6-dihydro-(11H)-benzo[c]quinolizine-3-one;

8-chloro-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

8-chloro-1-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one;

8-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

4-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis) and (trans);

8-chloro-4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

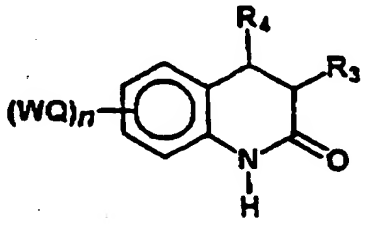
4,8-dimethyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

4,8-dimethyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis) and (trans);

8-chloro-4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis) and (trans).

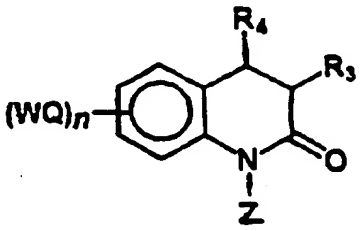
4. Process for the preparation of compounds according to Claim 1 wherein:

the amide-group of a compound of formula (2)



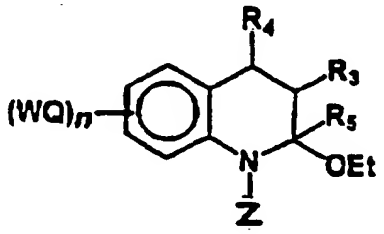
(2)

is protected with a protecting group Z to give the compound (3)



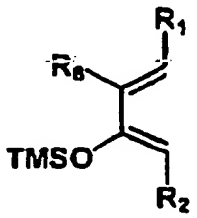
(3)

the above said compound (3) is reduced to compound (4), for example with sodium borohydride in ethanol (pH3)



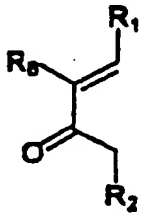
(4)

and compound (4) is reacted with a silylether (6)



(6)

prepared "in situ" by reacting a vinyl-ketone (5)



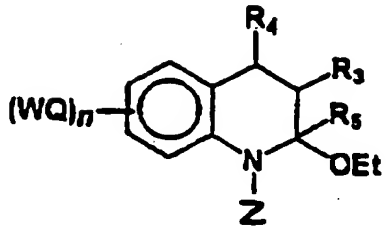
(5)

(wherein R_1, R_2, R_6 are as above defined) with a silylating agent as trimethylsilyltrifluorometansulphonic anhydride (TMSOTf) and are finally hydrolized, for example with sodium hydrogencarbonate, to give the final compound of formula (I) wherein X = O.

5. Process according to claim 4 wherein the possible introduction of the double bonds in position a or b is performed by reaction of dichlorodicianoquinone (DDQ) with the corresponding silylenolethers or by oxidation with quicksilver acetate of the saturated compound obtained as claimed above and the possible transformation of the group X is performed via the corresponding noltriflates and following carbonylation in the presence of palladium diacetate,

8 triphenylphosphine and the suitable nucleophilic reagent.

1 6. Compound of formula (4)



(4)

2 wherein W, Q, n, R_3, R_4, R_5 are as defined in claim 1 and Z is a
3 protecting group for the amide-group.

1 7. Pharmaceutical composition wherein the active principle is a
2 compound of formula (I) according to Claim 1 or mixtures thereof in
3 combination with the suitable pharmaceutical acceptable excipients.

1 8. Pharmaceutical composition according to Claim 7 for use in the
2 inhibition of the 5αR-I and/or 5αR-II iso-emzymes.

1 9. Pharmaceutical composition according to claims 7 and 8 in the form
2 suitable for topic use.

1 10. Use of a compound of formula (I) according to Claim 1 as a
2 medicament.

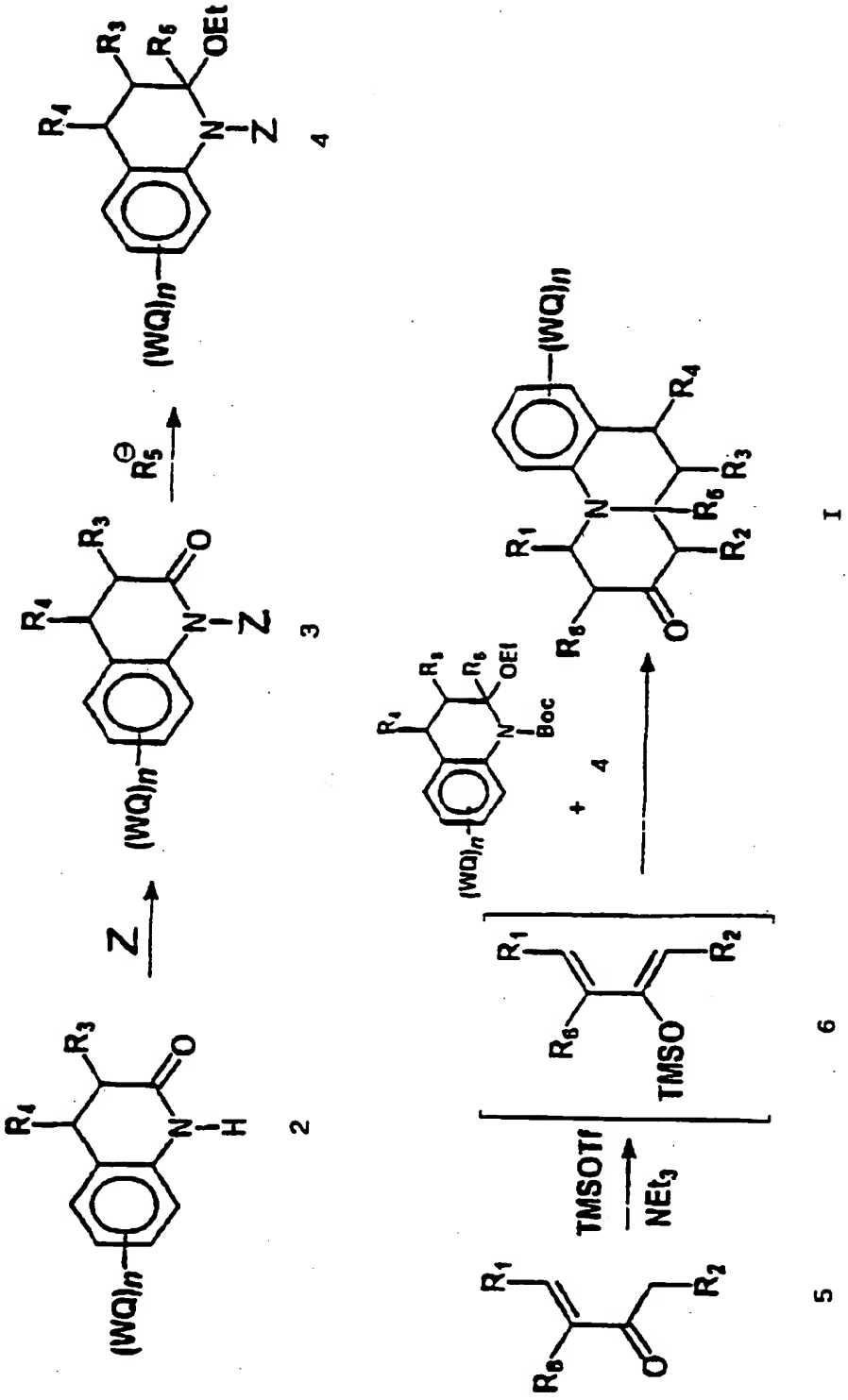
1 11. Use of a compound of formula (I) according to Claim 1 for the
2 preparation of a pharmaceutical composition for the treatment of acne,
3 baldness, prostatic cancer and prostatic hypertrophy in men and
4 hirsutism in women.

1 12. Method for the treatment of pathologies related to 5α-reductase
2 enzymes by administration to the patient of a pharmaceutically active
3 amount of a pharmaceutical composition according to Claims 7.

1 13. Method for treatment of acne, baldness, prostatic cancer and
2 prostatic hypertrophy in men and hirsutism in wom n, by administration

of a pharmaceutically active amount of a pharmaceutical composition according to Claims 7.

SCHEME


R3
R6
OEt
R4
N
Z
(WQ)n
4
R5⊖
3
O
2
H
Z
TMSOTf
NEt3
TMSO
R1
R2
R6
5
6
(WQ)n
Boc
OEt
+ 4
(WQ)n
R4
R3
R6
R2
R1
O
I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00552

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D455/04 C07D215/22 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 99, no. 25, 1983 Columbus, Ohio, US; abstract no. 212524t, page 646; column 1; XP002033587 see abstract	1
X	& SU 1 027 166 A (KIEV) 7 July 1983 ---	1
X	JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, vol. 3, 1979, LETCHWORTH GB, pages 584-590, XP002033586 R.MORRIN ACHESON ET AL.: "ADDITION REACTIONS OF HETEROCYCLIC COMPOUNDS.PART 67." see page 584 - page 588 ---	1
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 1997	11. 07. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00552

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 1 534 278 A (BRISTOL-MYERS.) 17 June 1968 see page 1 - page 5 -----	6

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/00552

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 12,13
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 97/00552

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 1534278 A		BE 702549 A	12-02-68
		CH 485724 A	15-02-70
		GB 1153818 A	29-05-69
		NL 6711207 A	16-02-68
		US 3455929 A	15-07-69